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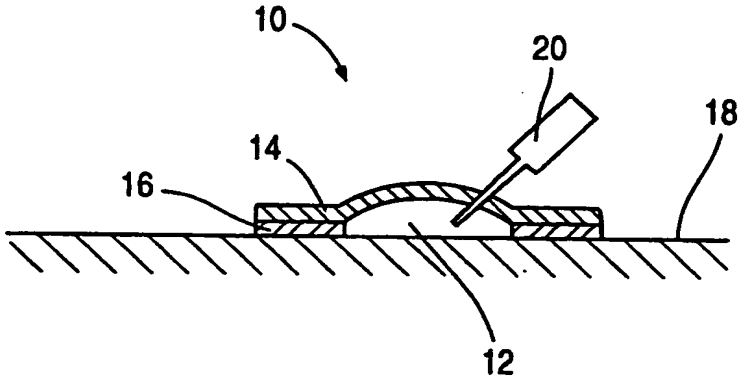
(54) Title: NONINVASIVE GLUCOSE MONITOR

(57) Abstract

This invention is a noninvasive glucose monitoring apparatus and method that does not rely upon heat, electricity or chemicals to collect glucose from interstitial fluid across the patient's skin. Moreover, the method and apparatus monitor blood glucose in real time, i.e., in a time period short enough to enable a diabetic to take appropriate action to correct blood glucose levels. A collection device (10) comprising a reservoir (12) containing a glucose collection medium such as water is placed against the stratum corneum of the patient's skin for a predetermined period of time. At least a portion of the glucose collection medium is removed from the reservoir at the end of the predetermined time and analyzed for glucose concentration.



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NONINVASIVE GLUCOSE MONITOR

Background of the Invention

This invention relates generally to methods and apparatus for glucose collection and concentration measurement. In particular, the invention is directed to a method and apparatus for monitoring blood glucose levels noninvasively through a patient's skin.

People suffering from diabetes mellitus must monitor blood glucose levels over the course of the day. The most common prior art method of measuring blood glucose levels is by actually drawing a portion of the subject's blood and performing a chemical analysis on the sample. Continually drawing blood creates safety risks for the patient, however.

The prior art has described "noninvasive" methods for measuring blood glucose levels. These supposedly noninvasive methods actually involve the application of chemicals, electricity, heat, or negative pressure to draw out body fluids other than blood that may nonetheless contain levels of glucose that correlate with blood glucose levels. For example, U.S. Patent No. 5,161,532 describes a glucose sensor that uses a pump to draw interstitial fluid out through the patient's skin into a sensor. The '532 patent states that any glucose in the interstitial fluid reacts with a chemical within the sensor to produce an electrical signal that is detected by a pair of electrodes.

U.S. Patent No. 5,036,861 describes a glucose monitor that collects the patient's sweat through a skin patch attached to the patient's wrist. Iontophoresis is

used to transdermally introduce a gel into the patient's skin. The gel contains a cholinergic agent for stimulating the secretion mechanism of the eccrine sweat gland and agents that minimize or prevent loss of glucose from the sweat as it travels from the sweat gland to the skin patch. As in the '532 patent, the device described in the '861 patent measures the glucose level in the collected sweat using electrodes.

U.S. Patent No. 5,139,023 describes yet another "noninvasive" apparatus and method for monitoring blood glucose. The monitor includes a glucose receiving medium such as water enclosed in a housing that holds the receiving medium against the patient's epithelial membrane. The glucose receiving medium includes a permeation enhancing chemical such as a natural bile salt that enhances glucose permeability from interstitial fluid across the epithelial membrane into the monitor. An attempt to collect glucose according to the '023 method and apparatus but without any permeation enhancing agent failed to show that any glucose was collected.

Finally, published European Patent Application EP 0 304 304 discloses a transdermal glucose detection system in which the detector contains a porous carrier saturated with detector chemicals. The detector adhesively attaches to the patient's skin. A membrane serves as a barrier to prevent migration of the detector chemicals out of the detector while permitting glucose to migrate into the detector. Interaction between glucose and the detector chemicals causes a perceivable color change over a six to twelve hour period. The device only detects the presence of glucose; it does not measure the actual amount of glucose in the detector.

Summary of the Invention

This invention provides a truly noninvasive glucose monitoring apparatus and method that does not rely upon heat, electricity or chemicals to collect glucose from interstitial fluid across the patient's skin. Moreover, the method and apparatus of this invention monitor blood glucose in real time, that is to say, in a time period short enough to enable a diabetic to take appropriate action to correct blood glucose levels.

In a preferred embodiment, a collection device comprising a reservoir containing a glucose collection medium such as water is placed against the stratum corneum of the patient's skin for a predetermined period of time. At least a portion of the glucose collection medium is removed from the reservoir at the end of the predetermined time and analyzed for glucose concentration.

Brief Description of the Drawings

Figure 1 is a side cross-sectional view of a glucose collection device according to the preferred embodiment of this invention.

Figure 2 is a bottom elevational view of the preferred glucose collection device.

Figure 3 is a cross-sectional view of a sensor for use with a glucose analysis method for use with this invention.

Figure 4 is a schematic representation of a glucose monitoring system according to this invention.

Detailed Description of the Preferred Embodiment

This invention presents a simple and noninvasive method for monitoring blood glucose levels. It is well-known that glucose can be found in a patient's

interstitial fluid and in a patient's sweat. Heretofore, however, it had been thought that glucose could not cross the patient's skin in a detectable amount in real time without the use of a permeability enhancer. See, e.g., U.S. Patent No. 5,139,023 at col. 7, line 3. It had also been thought that even when sweat or interstitial fluid is actively extracted from the patient, active pharmacological agents are needed to preserve the presence of glucose in the extracted sample. See, e.g., U.S. Patent No. 5,036,861, col. 3, lines 1-10.

This invention is a method and apparatus for detecting blood glucose in a truly noninvasive manner without actively extracting interstitial fluid from the patient and without the use of sweat inducers, glucose preservers or permeability enhancers. In a preferred embodiment, glucose is collected through the stratum corneum of the patient's skin by a reservoir containing a glucose collection medium. After the passage of a predetermined time period, the glucose collection medium is analyzed to measure the quantity of glucose present.

A preferred collection device for practicing this invention is shown in Figures 1 and 2. The device 10 comprises a reservoir 12 bordered by a cover 14, adhesive layer 16, and the stratum corneum of the patient's skin 18. As shown in part in Figure 2, the device is formed by attaching the plastic cover 14 to a double-sided adhesive 16 in which an oval or other-shaped hole has been formed. In the preferred embodiment, cover 14 is formed from cellophane plastic and adhesive layer 16 is Avery double-sided adhesive, part no. MED 3044.

The preferred glucose collection medium is distilled deionized water. According to the preferred method, the distilled deionized water is injected into reservoir 12 through a hypodermic needle and syringe 20. Despite suggestions to the contrary in the prior art,

glucose will migrate from the patient's interstitial fluid through the skin 18 and into the water within reservoir 12. After the water has rested against the patient's skin for a predetermined period of time, the water is withdrawn for analysis. This glucose collection device and method can collect glucose from the patient without the use of chemicals or mechanical extraction.

Alternatively, a hydrogel may be used as a collection medium. Suitable hydrogels are described in U.S. Patent No. 5,139,023.

Water (or other collection medium) from the reservoir may be extracted at periodic intervals (preferably in the range of 5 to 10 minutes) and analyzed to determine its glucose content. A preferred glucose analysis method is described by LaCourse et al. in "Optimization of Waveforms for Pulsed Amperometric Detection of Carbohydrates Based on Pulsed Voltammetry," 65 Analytical Chemistry 50-55 (1 January 1993), although other analysis methods may be used. The preferred pulse amperometric voltammetry (PAD) analysis method combines high performance liquid chromatography with electrochemical detection using bi-directional voltage waveforms. Specifically, water extracted from the reservoir is diffused onto a chromatography column. The column is washed with a high pressure solvent such as a NaOH solution. A stepped voltage waveform is applied across two electrodes in the solution, one of which is a gold rotating disk electrode. The voltage waveform has three parts: a detection potential in the range of -200 to +400 mV for greater than 40 ms detection period, an oxidation potential in the range of 300 to 800 mV for greater than approximately 60 ms, and a reduction potential in the range of -800 to +100 mV for greater than approximately 60 ms. A plot of electrode current at the gold electrode versus applied voltage yields a curve

with signature peaks at specific voltage values for certain solutes such as glucose. The peak amplitude or peak area are measures of the concentration of that solute.

An alternative glucose concentration analysis method is shown schematically in Figures 3 and 4. The glucose measurement technique of this embodiment is similar to the enzymatic technique described in U.S. Patent No. 5,165,407 and does not require the glucose collection medium to be extracted from the collection device.

A glucose sensor 30 is shown in detail in Figure 3. A sensor body 32 is received within a stainless steel hollow tubular needle 34. The sensor body includes a Teflon-coated platinum-iridium wire 36 (90% Pt/10% Ir) having a total O.D. of about 0.2 mm and a cavity 38 formed therein. Cavity 38 is approximately 1.0 mm in length and is located about 3.0 mm from the distal tip of the wire 36. A glucose oxidase layer 40 is immobilized within the cavity 38, and comprises a cellulose acetate polymer layer attached to the surface of the Pt-Ir wire, with glucose oxidase crosslinked through glutaraldehyde onto the cellulose acetate to form an indicating electrode. The procedure is described in more detail in U.S. Patent No. 5,165,407. The entirety of the indicating electrode is covered by a membrane 42 of polyurethane, also as described in U.S. Patent No. 5,165,407, to control the diffusion rate of glucose onto the indicating electrode.

Needle 34 has an aperture 44 adjacent its sharpened distal end 46 to expose layer 40. A silicone rubber plug 48 closes one end of the needle and a bead of epoxy 50 closes the other end, as shown. A plastic sheet 52 surrounding the proximal end of the needle serves as a holder.

Figure 4 is a schematic representation of a glucose collection and measurement system using this alternative glucose analysis method. The sensor 30 described above with reference to Figure 3 is inserted into a glucose collection device attached to the patient's skin 18 as described with reference to Figures 1 and 2 above so that the sensor's aperture 44 is exposed to the glucose collection medium 12. A conductor 60 leads from the indicating electrode of sensor 30 to a glucose measurement instrument 62. A second conductor 64 leads from a reference electrode 66 attached to the patient's skin 18. Instrument 62 applies a voltage across conductors 60 and 64; the current measured across the electrodes is related to the concentration of glucose in the collection medium in a manner known in the art.

The invention may be further explained through the following examples. The examples are not intended as a limitation to any claimed embodiment.

Examples 1-5

Glucose was collected from an adult human using an apparatus substantially similar to the apparatus shown in Figures 1 and 2. The device was attached to the stratum corneum of the skin on the patient's forearm, and the device's reservoir was initially filled with a sample consisting of 0.5 ml. of distilled deionized water via a hypodermic needle and syringe. The sample was withdrawn from the reservoir after five minutes and was replaced with a fresh sample of distilled deionized water at five minute intervals for a total of 30 minutes. The final sample remained in the reservoir for 30 minutes before being withdrawn and analyzed.

The withdrawn samples were analyzed using pulsed amperometric voltammetry. The results are shown

in Table I, with the glucose concentrations expressed in micromoles.

TABLE I

Sample	1	2	3	4	5
0-5 min	3.13μM	2.86μM	6.10μM	9.24μM	1.66μM
5-10 min	1.74 "	1.42 "	3.80 "	4.07 "	1.05 "
10-15 min	1.08 "	0.85 "	2.53 "	2.90 "	0.83 "
15-20 min	1.44 "	0.88 "	1.67 "	2.24 "	0.56 "
20-25 min	1.13 "	0.46 "	1.48 "	2.57 "	0.70 "
25-30 min	0.77 "	0.56 "	1.15 "	3.07 "	1.09 "
30-60 min	1.91 "	1.46 "	3.35 "	13.5 "	1.20 "

What is claimed is:

1. A noninvasive method of monitoring blood glucose across the skin of a patient without the use of a sweat inducer or a permeability enhancer, the method comprising the following steps:

placing a reservoir of a glucose collection medium adjacent the patient's skin; and

analyzing the glucose collection medium to measure the amount of glucose collected.

2. The method of claim 1 wherein the glucose collecting medium comprises water.

3. The method of claim 1 wherein the reservoir has an open side facing the patient's skin so that the glucose collection medium is in direct contact with the patient's skin.

4. The method of claim 1 wherein the reservoir comprises a glucose transfer membrane disposed between the glucose collection medium and the patient's skin.

5. The method of claim 1 wherein the analyzing step comprises pulsed amperometric detection.

6. The method of claim 1 wherein the analyzing step is performed at the end of a predetermined time period in the range of 5 to 10 minutes.

7. The method of claim 6 wherein the glucose collecting medium consists essentially of water.

8. The method of claim 7 further comprising the step of removing the glucose collection medium from the reservoir before the analyzing step.

9. The method of claim 8 wherein the analyzing step comprises pulsed amperometric detection.

10. The method of claim 1 wherein the analyzing step comprises exposing an glucose-responsive enzyme to the glucose collection medium, the enzyme being in contact with an indicating electrode.

11. A noninvasive method of collecting glucose from a patient across the skin of a patient without the use of a sweat inducer or a permeability enhancer, the method comprising the steps of placing a reservoir of a glucose collection medium adjacent the patient's skin for a period of time and removing at least a portion of the glucose collection medium from the reservoir.

12. A noninvasive method of collecting glucose from a patient across the skin of a patient without the use of a sweat inducer or a permeability enhancer, the method comprising the steps of placing a reservoir of a glucose collection medium adjacent the patient's skin and exposing a glucose-responsive enzyme to the glucose collection medium, the glucose-responsive enzyme being in contact with an indicating electrode.

13. A glucose collection device comprising:

a reservoir containing a glucose collection medium for collecting glucose from a patient in real time without the use of a permeability enhancer or a sweat inducer; and

means for attaching the device to a patient so that glucose can travel across the patient's skin.

14. The device of claim 13 wherein the glucose collection medium comprises water.

15. The device of claim 13 wherein the means for attaching comprises adhesive.

16. The device of claim 13 further comprising means for extracting the glucose collection medium from the reservoir without detaching the device from the patient.

17. A glucose monitoring system comprising:
a glucose collection device comprising
a reservoir containing a glucose collection medium for collecting glucose from a patient in real time without the use of a permeability enhancer or a sweat inducer and
means for attaching the device to a patient so that glucose can travel across the patient's skin; and
means for measuring the concentration of glucose within the glucose collection medium.

18. The glucose monitoring system of claim 17 wherein the means for measuring comprises a glucose-responsive enzyme in contact with the glucose collection medium, an indicating electrode in contact with the enzyme, a reference electrode in contact with the patient's skin, and an instrument in electrical contact with the indicating electrode and the reference electrode.

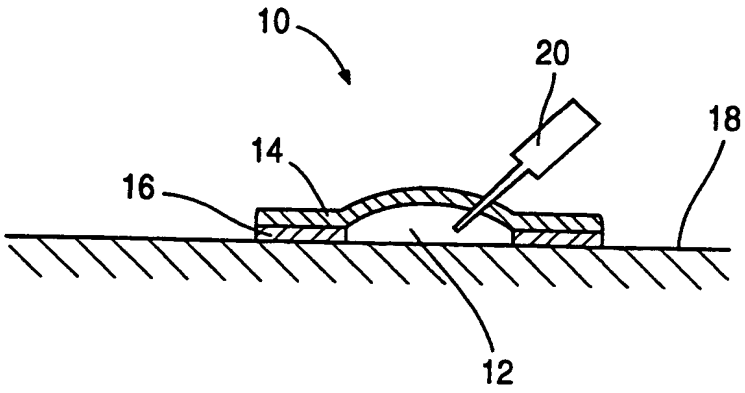

FIG. 1

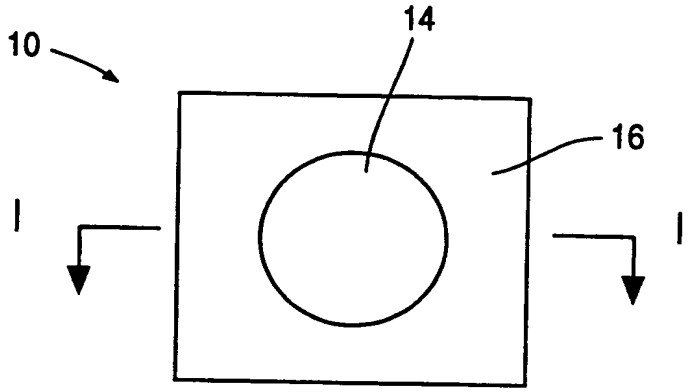

FIG. 2

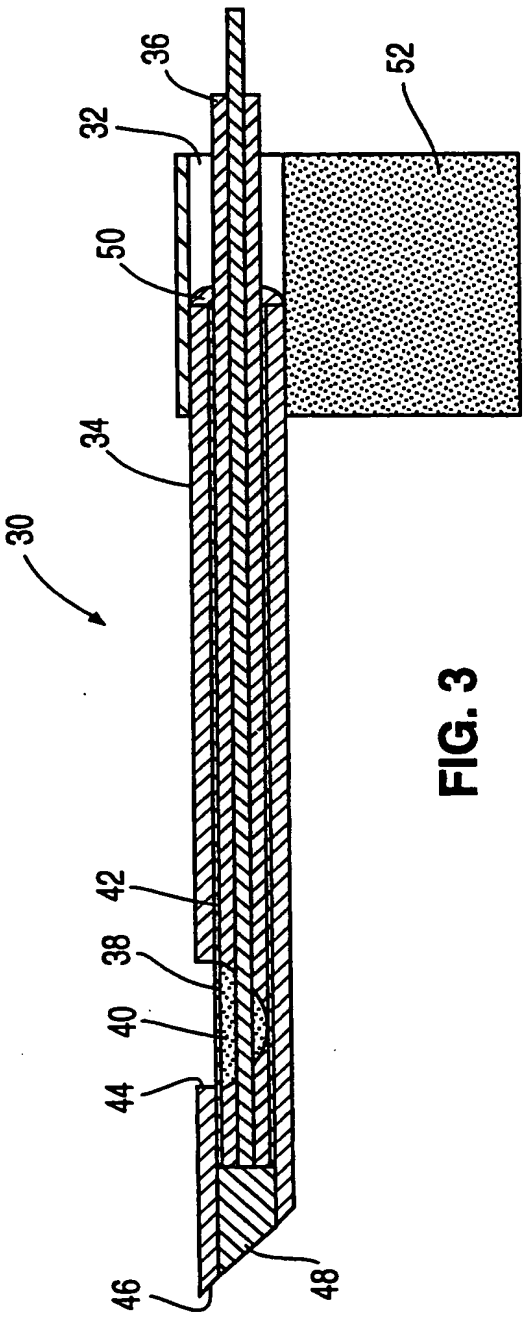

FIG. 3

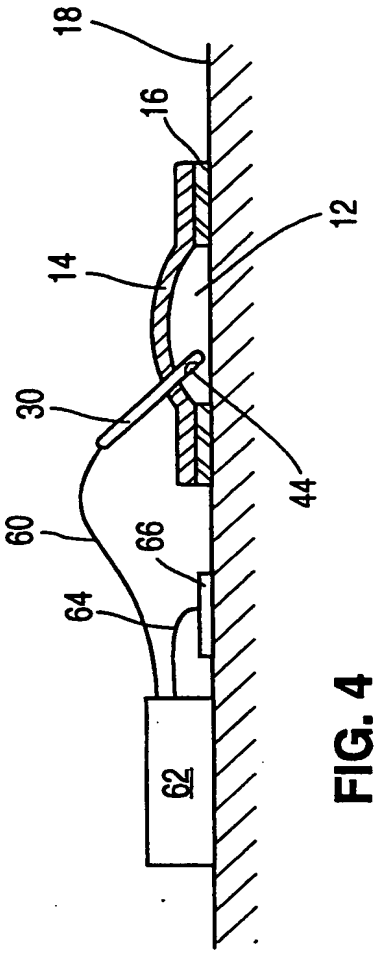

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/06684

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :A61B 5/00
US CL :128/632, 636, 760
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/632, 635-637, 760, 771; 422/58; 604/312, 328

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US, A, 5,076,273, (SCHOENDORFER ET AL.), 31 December 1991. See column 5 line 49 to column 6 line 48.	1, 4, 13, 15, 17 ---------- 2, 3, 5-13, 14, 16, 18
Y	US, A, 5,139,023, (STANLEY ET AL.), 18 August 1992. See column 14, lines 8-11.	2, 3, 5-9, 11, 14
Y	US, A, 5,056,521, (PARSONS ET AL.), 15 October 1991. See column 2, lines 21-24.	10, 12, 16, 18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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